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ORIGINAL ARTICLE

Presentation and Outcomes of Lassa Fever in Children in Nigeria: A Prospective Cohort Study (LASCOPE)

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Background. Data on the presentation, management, and outcomes of Lassa fever (LF) in children are limited.

Methods. Description of the clinical and biological features, treatment, and outcomes of reverse transcriptase and polymerase chain reaction (RT-PCR)-confirmed LF in children aged under 15, enrolled in the LASsa fever clinical COurse and Prognostic factors in an Epidemic context (LASCOPE) prospective cohort study in Nigeria between April 2018 and February 2023.

Results. One hundred twenty-four children (aged under 12 months: 19; over 12 months: 105) were hospitalized with RT-PCR-confirmed LF. All received intravenous ribavirin. During follow-up, 99/124 (80%) had fever; 71/124 (57%) had digestive symptoms, vomiting (n = 56/122, 46%) and abdominal pain (n = 34/78 aged ≥5 years, 44%) more often than diarrhea (n = 19/124, 15%); 17/124 (14%) had hemorrhagic signs; 44/112 (39%) had a hematocrit lower than 25%, of whom 32/44 (73%) received transfusions; 44/88 (50%) developed hypotension; 18/112 (16.1%) developed kidney disease improving global outcome (KDIGO) ≥2 acute kidney injury; 10/112 (8.9%) had KDIGO 3 acute kidney failure; 4/124 (3.2%) underwent renal replacement therapy. Seven children died, including 4 aged under 12 months (case fatality rate: under 12 months—22%, 95% confidence interval (CI): 7%–48%; over 12 months—2.9%, 95% CI: 0.7%–8.7%). In univariable analysis, age (P = .003), impaired consciousness (P = .026), and Lassa RT-PCR Ct value (P = .006) were associated with Day 30 mortality.

Conclusions. The fatality rate for children over 12 months hospitalized with LF was lower than that previously reported for adults. Hypotension and acute kidney injury were the most frequent organ dysfunctions. Bleeding was relatively infrequent. Anemia and the need for transfusion were common, the relative contribution of ribavirin-induced hemolysis being unknown.

Key words. acute kidney injury; anemia; children; Lassa fever; Nigeria; prognosis.

KEY POINTS

- Lassa fever fatality is lower in children over 12 months old than in adults.
- Upper gastrointestinal symptoms should prompt immediate testing in highly endemic areas.
- The frequent need for transfusion raises concern about the use of ribavirin.

INTRODUCTION

Lassa fever (LF) is a viral hemorrhagic fever caused by the *arenaviridae* Lassa virus, which is endemic in Western Africa. The country with the highest number of reported cases is Nigeria [1]. Despite reports of human-to-human transmission, notably

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in a nosocomial context [2], most infections originate from the rodent reservoir [3–5]. The World Health Organization (WHO) estimates that there are 300 000 LF cases and 5000 LF-related deaths every year [6], and considers LF a top-priority disease for research and development [7].

Previous studies have established that individuals of all ages, including children, can be infected by the Lassa virus [6, 8, 9] and develop a clinically overt disease [8, 10–13]. These studies also highlight the nonspecific clinical presentation of LF in children [8, 13, 14]. However, 50 years after the first descriptions of LF, prospective data on the clinical course, management, and outcomes of LF in children are still limited. Only a few retrospective studies, based on limited sample sizes, have reported data relating to children with reverse transcriptase and polymerase chain reaction (RT-PCR)-confirmed LF [15–17]. Pointing out distinctive features in LF clinical phenotype and course in children compared with adults is important to inform pediatricians practicing in endemic areas, who may have to suspect LF in a child consulting for an acute condition, as well as colleagues from other disciplines, who may have to manage a confirmed pediatric LF case.

This study reports the clinical presentation, management, and outcomes in children who took part in a prospective cohort study of LF in Nigeria.

METHODS

Patients and Setting

LASsa fever clinical COurse and Prognostic factors in an Epidemic context (LASCOPE) (NCT03655561) is a prospective cohort study conducted at the Federal Medical Centre Owo (FMCO), a tertiary hospital serving a large semi-urban and rural area in Ondo State, southwestern Nigeria. Its primary objective is to document the clinical features, management, outcomes, and associated factors in patients of all ages hospitalized with LF. The data relating to participants of the LASCOPE cohort aged under 15, enrolled between April 2018 and February 2023, are reported here.

Clinical Evaluation and Care

The LASCOPE study methods have been published previously [18, 19]. To summarize, all patients admitted to the FMCO with suspected LF were tested with the RealStar Lassa Virus RT-PCR kit 2.0 (Altona Diagnostics, Hamburg, Germany). All diagnostic tests were performed from total blood samples. RT-PCR-positive cases were referred to the LF ward. All children admitted to the LF ward were included in the cohort if their parents or guardians agreed to their participation and signed the informed consent form. The child's assent was also sought and documented for children aged 12 years and older.

Children with confirmed LF were managed according to the Nigerian guidelines [20]. All were started on intravenous ribavirin immediately after admission to the LF ward (Day 0), according to the following regimen: a 33 mg/kg loading dose on Day (D) 0, then 16 mg/kg every 6 h from D0 to D3 and 8 mg/kg every 8 h from D4 to D9 [21]. Standard supportive care was provided depending on the patient's clinical status. This included: oral or intravenous administration of fluids and electrolytes; analgesics; oxygen therapy for children with respiratory dysfunction; antimalarials for those with confirmed malaria; antibiotics for those with a suspected bacterial infection; whole blood transfusion for those with severe anemia; anticonvulsants for those with prolonged/recurrent seizures; intermittent hemodialysis for those with life-threatening acute kidney failure (AKF). noninvasive respiratory support, invasive hemodynamic monitoring, vasopressors, red blood cell/platelet concentrates, and plasma were not available.

Clinical monitoring included temperature, heart rate, noninvasive blood pressure, respiratory rate, pulse oxygen saturation (SpO2), and capillary glycemia. A 12-lead electrocardiogram was available if deemed necessary.

Routine biological monitoring included testing for malaria with a rapid diagnostic test (SD BIOLINE Malaria Ag P.f, Abbott, Chicago, IL, USA) or thick blood smear on D0. Physicians were encouraged to perform the following blood tests on D0, D5, and D10: full blood count, albumin, creatinine, urea, electrolytes, liver enzymes, and bilirubin. Additional tests were carried out as required, including another malaria rapid diagnostic test (RDT) in the event of unexplained prolonged/recurrent fever. Bacteriological analyses, including blood culture, and lactate and blood gas analysis were not available on a routine basis. Rapid tests for human immunodeficiency virus, hepatitis B virus, and hepatitis C virus were available at the clinician's request. Lumbar puncture was not performed.

The criteria for hospital discharge were the absence of fever or any other substantial symptoms, and completion of 10 days' ribavirin therapy. A negative Lassa RT-PCR test was not a mandatory criterion. Discharged children were asked to attend as an outpatient on D30. In case of no show, parents or guardian were contacted by phone and questioned about the vital status and clinical progress of their child.

Definitions

Between D0 and D30, trained research staff used a standard form to collect demographic, clinical, and biological characteristics on presentation and during follow-up, details of care and treatment received, and clinical outcomes.

Organ dysfunction was categorized as respiratory dysfunction, hypotension, impaired consciousness, or acute kidney dysfunction. Tachycardia and hypotension definitions were based on an age-specific threshold for heart rate and systolic blood pressure (SBP) (see Supplementary Material: Tables S1 and S2). Level of consciousness was categorized according to the

ACVPU classification: A = alert, C = confused, V = response to verbal stimulus, P = response to pain stimulus, U = unresponsive; impaired consciousness was defined as any category other than A. As confusion is difficult to ascertained in young children, categories A and C were merged, and considered as "normal consciousness" for this analysis. Respiratory dysfunction was defined as a SpO2 below 92% at room air. Acute kidney dysfunction was categorized as acute kidney injury (AKI) or AKF depending on the serum creatinine level (using age and gender-specific thresholds) and the need for dialysis components of the KDIGO staging [22] (see Supplementary Material: Table S3).

As abdominal pain, headache, dizziness, myalgia, chest/retrosternal pain, and sore throat are subjective patient/parent-reported symptoms, and therefore difficult to ascertain in young children, they are not reported in children below 5 in this analysis.

Malaria was defined as the presence of compatible signs and symptoms and either the presence of asexual forms of *Plasmodium* sp. on a thick blood smear, or a positive malaria RDT and no history of antimalarial treatment in the 4 weeks prior to admission.

The Lassa RT-PCR cycle threshold (Ct) values used in this analysis were those of the glycoprotein complex (GPC) gene target detected by the RealStar Lassa Virus RT-PCR kit 2.0.

Statistical Analysis

The frequency and proportion of qualitative variables, and the median and interquartile range (IQR) of quantitative variables, were described first at D0 ("on presentation"), then over the entire period in the hospital ("overall"), for the entire study population, then by age group (<12 months vs 1–14 years). The overall description included, for vital signs, severity criteria, and biological parameters, the poorest condition recorded at any time between D0 and death or discharge from hospital, and for signs and symptoms, those reported at least once between D0 and death or discharge from hospital. The poorest value for biological parameters was defined as (1) the highest value for plasma creatinine, urea, potassium, aspartate aminotransferase (AST), and alanine aminotransferase (ALT); (2) the lowest value for hematocrit, platelet count, plasma sodium, total carbon dioxide (tCO_2), albumin, and glucose. The denominator for each proportion calculation was the number of participants for whom data were available, unless otherwise stated. Kruskal–Wallis test was used to compare quantitative variables between age groups. Fisher's exact test was used to compare categorical variables between age groups, as well as to analyze the association between characteristics on presentation and D30 mortality. Due to the few numbers of fatal events and to the limited sample size, multivariable analysis was not performed. Data description and analysis were processed using SAS software, version 9.4.

Ethics and Data Protection

The study was approved by the Nigerian National Health Research Ethics Committee (protocol number NHREC/01/01/2007-14/05/2018). Confidentiality was guaranteed by de-identification and restricted access to study documents and databases.

RESULTS

Study Population

One hundred twenty-four participants (female $n = 62$, 50%), aged 1 day to 14 years (median 7 years; IQR 2.4–11 years) were included. They were admitted to the FMCO either by self-referral directly from their home ($n = 72$; 58%), by transfer from other public facilities ($n = 34$; 27%), or by transfer from a private clinic ($n = 18$; 15%). Overall, 87 (70%) were first admitted to the pediatric emergency department of the FMCO, and were then moved to the LF ward upon LF diagnostic confirmation; the remainder were admitted directly there without going through the emergency department. The median delay between the first symptom and admission to the LF ward was 8 days (IQR 5–11).

Clinical and Biological Presentation

The characteristics of the participants on presentation and during follow-up are given in Table 1 (see also Supplementary Material: Tables S4 and S4 bis). Fever was present in 99 children (80%). Digestive signs and symptoms were present in 56 children (45%) on presentation and 71 (57%) overall, with vomiting or abdominal pain being more common than diarrhea. At least 1 bleeding sign was present in 6 (4.8%) on presentation and 17 (14%) overall. Sixty-nine (56%) had at least 1 organ dysfunction, including hypotension ($n = 44/88$, 50%), ≥KDIGO 2 kidney dysfunction ($n = 18/112$, 16%), respiratory dysfunction ($n = 12/120$, 10%), and impaired consciousness ($n = 13$, 10%).

Among 8 neonates <1 month, 2 had facial swelling (both survived).

Overall, vomiting (16% vs 50%, $P < .005$) was less frequently observed in infants <12 months than in older children, contrary to respiratory dysfunction (41% vs 5%, $P < .001$).

Lassa RT-PCR Ct value was available for 100 participants, of whom 40 (40%) had a value of <30. The median Ct value was lower in infants <12 months than in older children (28 vs 33, $P = .038$). Regarding liver function tests, 26/83 (31%) had an AST level and 12/84 (14%) an ALT level over 3 times the upper limit of normal at least once during the period in the hospital; hyperbilirubinemia >27 µmol/L was found in only 2/57 (3.5%) children. On presentation, despite a similar proportion of ≥KDIGO 2 kidney dysfunction, infants <12 months more frequently had a plasma potassium >5 mmol/L (27% vs 6%, $P = .028$) and a metabolic acidosis (median plasma tCO_2 18 vs 22 mmol/L, $P = .009$) than did older children; they also had a

Table 1. Characteristics on Presentation and During Follow-up (*N* = 124)

	N[a]	On Presentation[b]	Entire Follow-up[c]
General			
Sex, *n* (%)	124		
Male		62 (50%)	-
Female		62 (50%)	-
Age, *n* (%)	124		
<1 month		8 (6.5%)	-
1–11 months		11 (8.9%)	-
1–4 years		27 (22%)	-
5–11 years		49 (40%)	-
12–14 years		29 (23%)	-
Vital parameters			
Level of consciousness, ACVPU, *n* (%)	124		
Alert or confused[d]		119 (96%)	111 (90%)
Voice (reactive to)		0 (0%)	1 (0.8%)
Pain (reactive to)		3 (2.4%)	7 (5.6%)
Unresponsive		2 (1.6%)	5 (4.0%)
Low systolic arterial pressure, *n* (%)[e]	88	12 (14%)	44 (50%)
Tachycardia, *n* (%)[e]	124	5 (4.0%)	18 (15%)
SpO2 <92% at room air, *n* (%)	120	4 (3.3%)	12 (10%)
Organ dysfunction score, *n* (%)[f]	124		
0		93 (75%)	55 (44%)
1		27 (22%)	54 (44%)
2[g]		4 (3.2%)	7 (5.6%)
3 or higher[g]		0 (0%)	8 (6.5%)
Other clinical signs and symptoms			
Fever (temperature >38.0°C), *n* (%)	124	99 (80%)	99 (80%)
Digestive symptom, any type, *n* (%)	124	56 (45%)	71 (57%)
Vomiting, *n* (%)	122	42 (34%)	56 (46%)
Abdominal pain[h], *n* (%)	78	24 (31%)	34 (44%)
Watery diarrhea, *n* (%)	124	16 (13%)	19 (15%)
Headache[h], *n* (%)	78	27 (35%)	31 (40%)
Dizziness[h], *n* (%)	78	13 (17%)	14 (18%)
Cough, *n* (%)	124	20 (16%)	30 (24%)
Myalgia[h], *n* (%)	78	1 (1.3%)	1 (1.3%)
Chest/retrosternal pain[h], *n* (%)	78	7 (9.0%)	8 (10%)
Sore throat[h], *n* (%)	78	4 (5.1%)	7 (9.0%)
Signs of encephalopathy, any type, *n* (%)	78	5 (6.4%)	12 (15%)
Seizure, *n* (%)	78	4 (5.1%)	8 (10%)
Meningeal syndrome, *n* (%)	78	1 (1.3%)	4 (5.1%)
Impaired hearing/tinnitus, *n* (%)	78	0 (0%)	0 (0%)
Impaired vision, *n* (%)	78	0 (0%)	0 (0%)
Hiccups, *n* (%)	124	1 (0.8%)	1 (0.8%)
Lower limb edema, *n* (%)	124	0 (0%)	3 (2.4%)
Facial swelling, *n* (%)	124	0 (0%)	3 (2.4%)
Bleeding, any type, *n* (%)	124	6 (4.8%)	17 (14%)
Macroscopic hematuria, *n* (%)	123	2 (1.6%)	9 (7.3%)
Melena, *n* (%)	122	0 (0%)	3 (2.4%)
Vaginal bleeding, *n* (%)[i]	19	0 (0%)	1 (5.3%)
Hematemesis, *n* (%)	124	2 (1.6%)	3 (2.4%)
Gingival bleeding, *n* (%)	124	1 (0.8%)	3 (2.4%)
Venous puncture point bleeding, *n* (%)	124	0 (0%)	0 (0%)
Conjunctival bleeding, *n* (%)	124	0 (0%)	0 (0%)
Epistaxis, *n* (%)	124	2 (1.6%)	3 (2.4%)
Hemoptysis, *n* (%)	124	0 (0%)	0 (0%)

Table 1. Continued

	N[a]	On Presentation[b]	Entire Follow-up[c]
Biology			
Blood Lassa RT-PCR Ct value[j], median (IQR)	100	32·4 (27.4–35.6)	-
<25, *n* (%)		19 (19%)	-
25–29.9, *n* (%)		21 (21%)	-
30–34.9, *n* (%)		29 (29%)	-
≥35, *n* (%)		31 (31%)	-
Hematocrit (%), median (IQR)	112	30 (27–34)	27 (23–30)
<25%[i], *n* (%)		20 (18%)	44 (39%)
<18%, *n* (%)		6 (5.4%)	10 (8.9%)
Platelets (G/L), median (IQR)	106	270 (147–396)	231 (119–363)
<80 G/L, *n* (%)		9 (8.5%)	14 (13%)
Plasma creatinine (µmol/L), median (IQR)	112	56 (41–79)	66 (46–85)
Elevated, *n* (%)		60 (54%)	70 (63%)
Plasma urea (mmol/L), median (IQR)	112	3.6 (2.6–4.7)	4·1 (3.2–4.8)
>8.0 mmol/L[k], *n* (%)		9 (8.0%)	11 (9.8%)
>20.0 mmol/L, *n* (%)		5 (4.5%)	5 (4.5%)
Acute kidney dysfunction[l], *n* (%)	112		
No dysfunction		89 (79%)	81 (72%)
KDIGO 1		9 (8.0%)	13 (12%)
KDIGO 2 (AKI)		7 (6.3%)	8 (7.1%)
KDIGO 3 (AKF)		7 (6.3%)	10 (8.9%)
Plasma sodium (mmol/L), median (IQR)	110	132.0 (128.2–137.0)	130.0 (126.0–135.0)
<128 mmol/L, *n* (%)		22 (20%)	36 (33%)
>145 mmol/L, *n* (%)		2 (1.8%)	4 (3.6%)
Plasma potassium (mmol/L), median (IQR)	111	4.10 (3.70–4.55)	4·50 (4.00–4.90)
<3.5 mmol/L, *n* (%)		17 (15%)	31 (28%)
>5.0 mmol/L, *n* (%)		10 (9.0%)	21 (19%)
Plasma chloride (mmol/L), median (IQR)	111	101.0 (98.0–104.0)	104.0 (102.0–107.5)
<98 mmol/L, *n* (%)		27 (24%)	38 (34%)
>108 mmol/L, *n* (%)		15 (14%)	22 (20%)
Plasma tCO_2 (mmol/L), median (IQR)	111	21.0 (18.0–24.0)	20.0 (17.0–23.0)
<18 mmol/L, *n* (%)		22 (20%)	29 (26%)
Anion gap[m], if tCO_2 <18 mmol/L, *n* (%)	21	16.7 (14.0–22.1)	-
>14 mmol/L		14 (66.7%)	-
≤14 mmol/L		7 (33.3%)	-
Plasma albumin (g/L), median (IQR)	72	33.5 (29.0–37.0)	32.0 (28.9–35.0)
<28 g/L, *n* (%)		15 (21%)	16 (22%)
Plasma glucose (mmol/L), median (IQR)	70	4.40 (3.60–5.38)	3.95 (3.18–4.80)
<3.0 mmol/L, *n* (%)		10 (14%)	14 (20%)
Plasma AST[n] (U/L), median (IQR)	83	74 (44–118)	79 (45–120)
>3 × ULN, *n* (%)		24 (29%)	26 (31%)
Plasma ALT[n] (U/L), median (IQR)	84	40 (26–67)	46 (33–72)
>3 × ULN, *n* (%)		11 (13%)	12 (14%)

ACVPU, Alert (A), Confused (C), responsive to Voice (V), responsive to Pain (P), Unresponsive (U); IQR, interquartile range.

[a]*N* = Number of patients with available value on presentation.

[b]On presentation = first available value from admission onwards.

[c]Entire follow-up: for vital signs and severity criteria: poorest condition recorded at any time from presentation to end of inpatient follow-up; for signs and symptoms: signs and symptoms reported at least once from presentation to end of inpatient follow-up; for biological values: poorest value recorded from presentation to end of follow-up. The poorest value for biological parameters was defined as (1) the highest value for plasma creatinine, urea, potassium, AST, and ALT; (2) the lowest value for hematocrit, platelet count, plasma sodium, tCO_2, albumin, and glucose.

[d]Considering the difficulty to assess confusion in young children, the Alert and Confused categories were merged.

[e]According to the age-specific threshold (see Supplementary Appendix Table S1).

[f]Organ dysfunctions were: hemodynamic dysfunction, respiratory dysfunction, impaired consciousness, and acute kidney dysfunction (see Supplementary Appendix Table S2).

[g]Combinations of organ dysfunctions for the entire follow-up were: impaired consciousness plus respiratory (*n* = 4), hemodynamic plus renal (*n* = 2), respiratory plus renal (*n* = 1), impaired consciousness plus respiratory plus renal (*n* = 3), impaired consciousness plus respiratory plus hemodynamic (*n* = 1), hemodynamic plus respiratory plus renal (*n* = 1), and impaired consciousness plus hemodynamic plus respiratory plus renal (*n* = 4).

[h]For some subjective patient or parent-reported symptoms that are difficult to assess in very young children, the analysis was restricted to children aged 5 or older.

[i]Of the 19 girls aged >12.

[j]Ct = Cycle threshold for the Lassa Virus RT-PCR, GPC gene target (RealStar Lassa Virus RT-PCR kit 2.0, Altona, Hamburg, Germany), 24 (19%) participants had a positive RT-PCR test result but unknown Ct value.

[k]Categorization is inclusive: "Hematocrit <25%" includes participants with an hematocrit <18%; "Urea > 8 mmol/L" includes participants with an urea >20 mmol/L.

[l]AKI, acute kidney injury; AKF, acute kidney failure; KDIGO, kidney disease—improving global outcome. Age and gender-specific threshold for the upper limit of reference interval for serum creatinine (see Supplementary Appendix).

[m]Anion gap formula (mmol/L): (natremia + kalemia)—(chloremia + tCO_2).

[n]AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal range. Missing values for transaminases are for patients included while the biology device used for liver function testing was out of order or there was a shortage of reagent.

higher proportion of severe hypoglycemia <3 mmol/L (63% vs 8%, $P < .001$), than did their counterparts. A urinalysis test was carried out on 13 participants on admission and showed proteinuria ≥2+ in 4 (31%) and hematuria ≥2+ in 2 (15%).

Severe anemia with hematocrit <18% was present in 6/112 (5.4%) children on presentation, of whom 5/6 (83%) declared having had a recent positive malaria test (within 4 weeks prior to admission), and 2/6 (33%) still had a positive thick blood smear on admission. Four additional participants had hematocrit >18% on presentation and <18% later on, of whom 2 presented bleeding and 3 had a malaria diagnosis from admission onwards.

Treatment

The care and treatment administered are detailed in Table 2. Four participants (3.2%) had already started on ribavirin prior to admission to the LF ward. All were given ribavirin after admission.

Fifty-nine children (48%) had had a positive malaria test result, without further information regarding the type of test, and 92 (74%) had been treated for suspected or documented malaria in the 4 weeks leading up to admission. From admission onwards, 58 (47%) children had a malaria diagnostic test performed (thick blood smear $n = 39$; rapid diagnostic test $n = 33$), the results of which were positive for 39/58 (67%) (see Supplementary Material: Table S5 for further details on test types and results); and 51 (41%) were given antimalarial drugs during their stay in hospital.

Four out of 10 children who developed KDIGO stage 3 AKF underwent renal replacement therapy: one 7-year-old boy weighing 20 kg (1 session, survived), one 11-year-old girl

Table 2. Care and Treatments (*N* = 124)

	N	
Length of hospital stay (days), Median (IQR)		
People who were discharged alive[a]	120	11.0 (10.0–13.0)
People who died at the hospital	4	2.50 (0.75–4.50)
Admission in the intensive care unit[b] of the LF ward, *n* (%)	124	14 (11%)
Ribavirin therapy		
Received, *n* (%)	124	124 (100%)
Time between first symptoms and first dose (days), median (IQR)	119	8 (5–11)
Cumulated dose received (mg/kg), median (IQR)	118	443 (403–469)
Oxygen		
Received, *n* (%)	102	18 (18%)
Duration (days), median (IQR)	18	3.00 (2.00–9.00)
Total blood transfusion		
Received, *n* (%)[c]	124	52 (42%)
Number of units (total blood pints), median (IQR)	37	1.00 (1.00–2.00)
Renal replacement therapy (intermittent hemodialysis)		
Received, *n* (%)	124	4 (3.2%)
Indications, *n* (%)[d]		
Symptomatic hyperazotemia	2	
Fluid overload, no response to diuretics	1	
Unknown	1	
IV fluids		
Received, *n* (%)	124	124 (100%)
Cumulated volume received (mL/kg) overall, median (IQR)	118	276 (95–500)
Cumulated volume received (mL/kg) according to SBP on presentation	83	
SBP ≥ age-specific threshold, median (IQR)	71	286 (144–414)
SBP < age-specific threshold, median (IQR)	12	460 (212–610)
Duration under IV fluids (days), median (IQR)	111	7.0 (5.0–10.0)
Antibacterial therapy		
Received, *n* (%)	124	103 (83%)
Duration (days), median (IQR)	103	9.0 (7.0–11.0)
Antimalarial therapy		
Received, *n* (%)[e]	124	51 (41%)

[a]Of whom 3 died after discharge.

[b]Intensive care unit refers to a specific area of the Lassa ward where patients were more frequently monitored for vital functions. Mechanical ventilation, vasopressive drugs, and invasive hemodynamic monitoring were not available.

[c]Number of participants transfused among the 124 with available data, and median (IQR) number of blood pints received among the 37 transfused participants with available data. Thirty-two (63%) and 9 (18%) of those transfused had a minimal hematocrit <25% and <18%, respectively.

[d]One missing data.

[e]Antimalarial therapy administered within the Lassa ward (treatments prior to admission are not included).

weighing 45 kg (4 sessions, survived), one 12-year-old girl weighing 28 kg (1 session, died soon after start of dialysis), and one 11-year-old girl weighing 57 kg (unknown number of sessions, died after discharge from hospital). Among the 6 children with KDIGO stage 3 who did not receive renal replacement therapy, a 12-year-old boy died the day he was admitted to the Lassa ward, and the 5 others (aged 2, 4, 5, 8, and 11 years) survived.

18/102 (18%) children with information available were given supplemental oxygen. Finally, all received IV fluids, with a median cumulated volume over the hospital stay of 276 mL/kg (95–500) (not including transfusions).

52 (42%) were given whole blood transfusions, of whom 32/52 (62%) and 9/52 (17%) had a minimal hematocrit of <25% and <18%, respectively. In univariable analysis, there was no association between transfusion and declared positive malaria diagnostic test within 4 weeks prior to admission ($P = .8$), declared antimalarial treatment within 4 weeks prior to admission ($P = .14$), and malaria diagnosis from admission onwards ($P = .3$) (see Supplementary Material: Table S6).

Mortality

Seven children died (1 missing outcome, overall case fatality rate (CFR) 5.7%; 95% CI 2.5–11.8), 5 of them being girls. Of the 7 who died, 4 did so during their stay in the hospital (1 aged 1 day, 1 aged 4 months, and 2 aged 12 years), 2 of these within 24 h of admission, 1 on D4, and 1 on D6. The other 3 died (unknown cause of death) within 10 days of being discharged from the hospital, between D21 and D23 post-admission: 1 aged 3 days on admission died at the age of 3 weeks, 1 aged 15 days on admission died at the age of 5 weeks, the latter died at the age of 11 years.

In univariable analysis, age ($P = .003$), impaired consciousness ($P = .026$), and low Lassa RT-PCR Ct value ($P = .006$) on presentation were associated with the risk of death between D0 and D30 (see Table 3).

DISCUSSION

A few retrospective studies with limited sample sizes have been carried out using data collected on children with RT-PCR-confirmed LF; the results of these studies have varied in terms of the CFRs reported [15–17]. This is the first cohort study to provide a prospective estimation of LF CFR and a comprehensive description of the clinical and biological characteristics of the disease in children hospitalized with RT-PCR-confirmed LF. All participants received the optimal standard of care, including intravenous ribavirin, oxygen therapy, whole blood transfusion, and dialysis where appropriate.

Twenty-two percent of the children aged under 12 months and 2.9% of those aged 12 months or over died. The CFR in children aged 12 months and over was lower than that reported in 2 recent retrospective pediatric studies conducted in Nigeria and Sierra Leone [16, 17]. It was also lower than the CFR in adults estimated by a recent analysis from the LASCOPE cohort study at 13% [18]. This is consistent with the mortality rate being lower in children than in adults, as reported in historical LF studies prior to the RT-PCR era [10, 23, 24]. The high CFR in children under 12 months old, and even more higher in those under 1 month, should be interpreted with caution since there are few participants in these age groups. However, it is not surprising that mortality should be much higher in infants and more particularly in neonates than in older children, since the appropriate care is more difficult to administer in severe cases. Appropriate monitoring, including early recognition of the clinical signs of shock (cold extremities, prolonged capillary refill time, weak pulse, etc.), and invasive treatment procedures (vascular access, intermittent hemodialysis, etc.) can be particularly challenging, if not impossible, in those below 1 year.

After fever, the most frequent clinical features were digestive disorders [8, 14, 25–28]. Symptoms of the upper gastrointestinal tract were more common than those of the lower tract. Some authors reported an association between the presence of vomiting and a positive LF test result in febrile children seeking hospital care in a highly endemic area of Nigeria [29]. LF can mimic pediatric abdominal emergencies such as intestinal intussusception, peritonitis, and can even be associated with a genuine acute appendicitis [26, 28]. Clinicians caring for children in LF endemic areas, including surgeons, should therefore maintain a high index of suspicion where there is vomiting or abdominal pain. Invasive management of LF-infected patients without proper barrier measures could expose other patients, healthcare staff, and relatives to the risk of nosocomial transmission [2].

The "swollen baby syndrome," is often considered as a classical and pejorative clinical presentation of pediatric Lassa fever, even though it has only been mentioned once in a small retrospective cohort conducted in Liberia in 1987 [23]. In the study by Monson and colleagues, among 33 children with LF diagnosed by serology, 4 died, of whom 3 presented with this syndrome. In the present prospective study, 4 infants <12 months died but none had facial swelling, and the 2 neonates with facial swelling survived. Also, sore throat, which is often considered as a common sign in patients with LF, was infrequently reported here.

Of note, hearing and vision impairment were not reported at all in this analysis. Neurosensorial hearing loss is considered as a classic feature in LF. Actually, due to the lack of baseline evaluation, the incidence of this complication is difficult to assess in a reliable way in adult patients with LF, and it is of course even more difficult in children. Therefore, it may have been underestimated.

More than half the children had a low SBP at least once during their hospital stay, which is almost 3 times the rate previously reported by the LASCOPE cohort for adults [18]. Conversely,

Table 3. Association Between Mortality (Day 0 to Day 30) and Characteristics on Presentation, Univariable Analysis (*N* = 123)

Characteristic	Missing		*N*	Died	(%)	*P*[a]
Sex[b]	0	Female	62	5	8.1	.4
		Male	61	2	3.3	
Age	0	<1 month	7	3	42.9	**.003**
		1–12 months	11	1	9.1	
		1–4 years	27	0	0	
		5–11 years	49	1	2.0	
		12–14 years	29	2	6.9	
Symptoms onset to admission	4	≤7 days	53	3	5.7	.7
		>7 days	66	2	3.0	
Tachycardia	0	No	118	6	5.1	.3
		Yes	5	1	20	
Hypotension	35	No	76	4	5.3	.9
		Yes	12	0	0	
SpO2 under room air	4	≥92	115	5	4.3	.9
		<92	4	0	0	
Organ dysfunction score	0	0	92	4	4.3	.2
		1	27	2	7.4	
		≥2	4	1	25	
Impaired consciousness	0	No	118	5	4.2	**.026**
		Yes	5	2	40	
Signs of encephalopathy	0	No	73	2	2.7	.2
		Yes	5	1	20	
Digestive symptoms	0	No	67	4	6.0	.9
		Yes	56	3	5.4	
Bleeding	0	No	117	6	5.1	.3
		Yes	6	1	17	
Hematocrit	12	≥25%	91	4	4.4	.3
		<25%	20	2	10	
KDIGO stage	12	<2	97	4	4.1	.2
		≥2	14	2	14	
AST	41	<3 ULN	58	1	1.7	.2
		≥3 ULN	24	2	8.3	
ALT	40	<3 ULN	72	2	2.8	.4
		≥3 ULN	11	1	9.1	
Blood Lassa RT-PCR Ct	24	≥35	31	1	3.2	**.006**
		30–34	28	1	3.6	
		25–29	21	0	0	
		<25	19	5	26	

KDIGO, kidney disease—improving global outcome stage; RT-PCR Ct, Cycle threshold value for the Lassa Virus RT-PCR, GPC gene target (RealStar Lassa Virus kit 2.0®, Altona, Hamburg, Germany).

[a]*P* value for Fisher exact test.

[b]One male participant was excluded because of missing data for vital status.

low SpO2 (10%) and bleeding (14%) were relatively infrequent. This suggests that endothelial dysfunction—a hallmark of LF disease—and some of its consequences, among which bleeding or fluid extravasation leading to pulmonary edema and hypotension [30], might be less common in children than in adults. An implication of such a high proportion of low SBP is that clinicians treating children with Lassa fever must closely monitor the hemodynamic status as well as the input-output balance, in order to reactively adjust fluid and electrolytes intake and prevent the occurrence of cascading organs dysfunctions. In future studies, clinical examination supported by point-of-care thoracic ultrasound and echocardiography should help describe the respiratory and hemodynamic function in children with LF in more detail [31, 32].

Clinicians should also be particularly careful regarding the risk of severe hyperkalemia and hypoglycemia on presentation, 2 life-threatening conditions that could occur more frequently in infants below 1 year and require immediate corrective measures.

The incidence of severe anemia was high, with 40% of the children receiving blood transfusions. There are several possible causes of anemia in severe acute systemic viral diseases with hemorrhagic potential. In West Africa, this includes sickle cell anemia in particular. Unfortunately, it was possible neither to

document this chronic condition reliably, nor to explore further the many other possible causes of anemia (eg, iron and micronutrients deficiency, malnutrition, repeated bouts of malaria, coincidental parasitic infections, etc.) for the present study. Also, the design of the study did not allow further investigation of the relative contribution of ribavirin toxicity, which remains a concern with LF patients of all ages.

Kidney dysfunction was common, with 16% and 9% of children being staged KDIGO ≥2 and KDIGO 3, respectively. These figures are similar to those found in adults in the LASCOPE cohort [18], and lower than those reported in children in retrospective cohort studies conducted in Nigeria [16] and Sierra Leone [17].

Convulsion is common in children under 5 with acute febrile illnesses, including LF [29]; it is therefore unsurprising that seizure was the most common sign of encephalopathy in the present study. In care centers that provide treatment for high-consequence infectious diseases, rapid access to patients with acute complications may be problematic. In this context, the use of second-line anti-seizure medication, which has the advantage of being easier to administer and having fewer respiratory depressant side effects, may be considered [33]. The frequency of both seizures and signs of encephalopathy in the children in this study was similar to that previously reported in adults with LF [18], suggesting that the neurotropism of the Lassa virus might not be very different across age groups.

The Nigerian guidelines for LF case management [20] recommend the use of ribavirin for all age groups. Ribavirin has long been considered the gold standard treatment for LF but is becoming increasingly controversial [34, 35]. The efficacy of ribavirin in LF has been the subject of only 1 non-randomized trial, which did not involve children [21]. The WHO now emphasizes that there is currently insufficient evidence on ribavirin efficacy in LF [36]. The aim of this study was not to provide evidence regarding the efficacy or toxicity of ribavirin. However, the important increase in the proportion of children with anemia from presentation to discharge call for an evaluation of the contribution of ribavirin-induced hemolytic anemia, among other causes, and for more study of the benefit/risk ratio of ribavirin in children. In a general way, it should be a priority to include children in future clinical trials evaluating the safety, tolerability, and efficacy of innovative therapeutic strategies for LF.

The clinical presentation of LF being febrile and aspecific, it can mimick many common acute febrile illnesses. Of note, the Nigerian national guidelines for the management of Lassa fever recommend the empirical administration of antibiotics to Lassa patients who are severely ill, as well as to pregnant women (especially when the fetus is dead) [20]. In daily practice, broad-spectrum antibiotics are often started on a presumptive basis upon admission in many patients with LF, as illustrated by this analysis. Diagnostic tests for potential coinfections were not available on a routine basis at the FMCO, except for malaria. As a consequence, most participants received empirical antimicrobials. The limited capacity to perform microbiological investigations in many Subsaharan Africa health facilities, notably bacterial culture, as well as the necessity to perform such tests under BLS3 conditions in the case of patients with VHFs, contribute to the overprescription of antibiotics. In the context of the rising prevalence of antimicrobial resistance but low awareness about its negative consequences among healthcare workers in Nigeria [37], it is of paramount importance to develop innovative, easy-to-use, and affordable diagnostic tools to guide antibiotics prescription [38], as well as antimicrobial stewardship programs [38, 39]. It is also important to address misconceptions regarding the fear of contamination among healthcare workers, notably, those specialists who are not involved in the daily management of patients with LF [40], so that appropriate diagnostic procedures can be performed more systematically when required, eg, lumbar puncture by neurologists in patients with encephalopathy or meningeal syndrome.

In conclusion, LF is common in children in endemic areas, with aspecific clinical manifestations potentially involving the risk of nosocomial transmission. The disease seems particularly severe in newborns and infants under 12 months old. In children aged 12 months and over, even if the CFR seems lower than in adults, it can lead to kidney dysfunction, requiring dialysis, and severe anemia, requiring blood transfusion. The issue of ribavirin's risk/benefit ratio should be a research priority in the pediatric population. This study also highlights the importance of designing LF treatment units that are suitable for healthcare workers to treat the specific needs of children. This includes facilitating continuous, but safe contact between children and their parents.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

Notes

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

REFERENCES

1. Nigeria Centre for Disease Control. An update of Lassa fever outbreak in Nigeria [Internet]. https://ncdc.gov.ng/diseases/sitreps/?cat=5&name=An%20update%20of%20Lassa%20fever%20outbreak%20in%20Nigeria. [cited 2023 Feb 13].
2. Dan-Nwafor CC, Ipadeola O, Smout E, et al. A cluster of nosocomial Lassa fever cases in a tertiary health facility in Nigeria: description and lessons learned, 2018. Int J Infect Dis **2019**; 83:88–94.
3. Lo Iacono G, Cunningham AA, Fichet-Calvet E, et al. Using modelling to disentangle the relative contributions of zoonotic and anthroponotic transmission: the case of Lassa fever. PLoS Negl Trop Dis **2015**; 9:e3398.
4. Kafetzopoulou LE, Pullan ST, Lemey P, et al. Metagenomic sequencing at the epicenter of the Nigeria 2018 Lassa fever outbreak. Science **2019**; 363:74–7.
5. Siddle KJ, Eromon P, Barnes KG, et al. Genomic analysis of Lassa virus during an increase in cases in Nigeria in 2018. N Engl J Med **2018**; 379:1745–53.
6. McCormick JB, Webb PA, Krebs JW, Johnson KM, Smith ES. A prospective study of the epidemiology and ecology of Lassa fever. J Infect Dis **1987**; 155:437–44.
7. WHO. *A research and development Blueprint for action to prevent epidemics [Internet]*. WHO. http://www.who.int/csr/research-and-development/en/. [cited 2016 Oct 9].
8. Sharp PC. Lassa fever in children. J Infect **1982**; 4:73–7.
9. Yalley-Ogunro JE, Frame JD, Hanson AP. Endemic Lassa fever in Liberia. VI. Village serological surveys for evidence of Lassa virus activity in Lofa County, Liberia. Trans R Soc Trop Med Hyg **1984**; 78:764–70.
10. Frame JD. Clinical features of Lassa fever in Liberia. Rev Infect Dis **1989**; 11:S783–9.
11. Monath TP, Maher M, Casals J, Kissling RE, Cacciapuoti A. Lassa fever in the Eastern Province of Sierra Leone, 1970-1972. II. Clinical observations and virological studies on selected hospital cases. Am J Trop Med Hyg **1974**; 23:1140–9.
12. Carey DE, Kemp GE, White HA, et al. Lassa fever. Epidemiological aspects of the 1970 epidemic, Jos, Nigeria. Trans R Soc Trop Med Hyg **1972**; 66:402–8.
13. White HA. Lassa fever A study of 23 hospital cases. Trans R Soc Trop Med Hyg **1972**; 66:390–401.
14. Webb PA, McCormick JB, King IJ, et al. Lassa fever in children in Sierra Leone, West Africa. Trans R Soc Trop Med Hyg **1986**; 80:577–82.
15. Okokhere P, Colubri A, Azubike C, et al. Clinical and laboratory predictors of Lassa fever outcome in a dedicated treatment facility in Nigeria: a retrospective, observational cohort study. Lancet Infect Dis **2018**; 18:684–95.
16. Adetunji AE, Ayenale M, Akhigbe I, et al. Acute kidney injury and mortality in pediatric Lassa fever versus question of access to dialysis. Int J Infect Dis **2021**; 103:124–31.
17. Samuels RJ, Moon TD, Starnes JR, et al. Lassa fever among children in eastern province, Sierra Leone: a 7-year retrospective analysis (2012–2018). Am J Trop Med Hyg **2021**; 104:585–92.
18. Duvignaud A, Jaspard M, Etafo IC, et al; LASCOPE study group. Lassa fever outcomes and prognostic factors in Nigeria (LASCOPE): a prospective cohort study. Lancet Glob Health **2021**; 9:e469–78.
19. Duvignaud A, Jaspard M, Etafo IC, et al. Lassa fever clinical course and setting a standard of care for future randomized trials: a protocol for a cohort study of Lassa-infected patients in Nigeria (LASCOPE). Travel Med Infect Dis **2020**; 36:101557.
20. Nigeria Centre for Disease Control. *National guidelines for Lassa fever case management [Internet]*. Nigeria Centre for Disease Control; **2018**. https://ncdc.gov.ng/themes/common/docs/protocols/92_1547068532.pdf. [cited 2023 Feb 13].
21. McCormick JB, King IJ, Webb PA, et al. Lassa fever. Effective therapy with ribavirin. N Engl J Med **1986**; 314:20–6.
22. Kidney Disease | Improving Global Outcome. *KDIGO clinical practice guideline for acute kidney injury*. Kidney International Supplements [Internet]; **2012**; Vol 2. https://linkinghub.elsevier.com/retrieve/pii/S2157171615310388. [cited 2020 Jul 1].
23. Monson MH, Cole AK, Frame JD, Serwint JR, Alexander S, Jahrling PB. Pediatric Lassa fever: a review of 33 Liberian cases. Am J Trop Med Hyg **1987**; 36:408–15.
24. Shaffer JG, Schieffelin JS, Grant DS, et al.; Viral Hemorrhagic Fever Consortium. Data set on Lassa fever in post-conflict Sierra Leone. Data Brief **2019**; 23:103673.
25. Sandige H. Learning in the Lassa Belt. Am J Trop Med Hyg **2018**; 99:1110–1.
26. Akpede GO, Adetunji AE, Udefiagbon EO, et al. Acute abdomen in pediatric patients with Lassa fever: prevalence and response to nonoperative management. J Pediatr Infect Dis Soc **2018**; 8:519–24.
27. Akhiwu HO, Yiltok ES, Ebonyi AO, et al. Lassa fever outbreak in adolescents in North Central Nigeria: report of cases. J Virus Erad **2018**; 4:225–7.
28. Dongo AE, Kesieme EB, Iyamu CE, Okokhere PO, Akhuemokhan OC, Akpede GO. Lassa fever presenting as acute abdomen: a case series. Virol J **2013**; 10:123.
29. Akhuemokhan OC, Ewah-Odiase RO, Akpede N, et al. Prevalence of Lassa Virus Disease (LVD) in Nigerian children with fever or fever and convulsions in an endemic area. PLoS Negl Trop Dis **2017**; 11:e0005711.
30. Horton LE, Cross RW, Hartnett JN, et al. Endotheliopathy and platelet dysfunction as hallmarks of fatal Lassa fever. Emerg Infect Dis **2020**; 26:2625–37.
31. Singh Y, Tissot C, Fraga MV, et al. International evidence-based guidelines on Point of Care Ultrasound (POCUS) for critically ill neonates and children issued by the POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). Crit Care **2020**; 24:65.
32. Yacoub S, Lang HJ, Shebbe M, et al. Cardiac function and hemodynamics in Kenyan children with severe malaria. Crit Care Med **2010**; 38:940–5.
33. Lyttle MD, Rainford NEA, Gamble C, et al.; Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet **2019**; 393:2125–34.
34. Eberhardt KA, Mischlinger J, Jordan S, Groger M, Günther S, Ramharter M. Ribavirin for the treatment of Lassa fever: a systematic review and meta-analysis. Int J Infect Dis **2019**; 87:15–20.
35. Salam AP, Cheng V, Edwards T, Olliaro P, Sterne J, Horby P. Time to reconsider the role of ribavirin in Lassa fever. PLoS Negl Trop Dis **2021**; 15:e0009522.
36. World Health Organization. Health Topics: Lassa fever [Internet]. https://www.who.int/health-topics/lassa-fever#tab=tab_3. [cited 2023 Feb 13].
37. Yusuf I, Arzai AH, Yusha UM, Garba L, Haruna M, Getso MI. Cross-sectional survey of knowledge and attitudes of healthcare workers and community members toward the Ebola virus disease and antimicrobial resistance pathogens outbreaks in Nigeria. Pan Afr Med J **2021**; 40:116.
38. Iroh Tam PY. The challenge and opportunity of pediatric antimicrobial stewardship in low resource settings. J Trop Pediatr **2020**; 66:1–3.
39. Gulumbe BH, Danlami MB, Abdulrahim A. Closing the antimicrobial stewardship gap - a call for LMICs to embrace the global antimicrobial stewardship accreditation scheme. Antimicrob Resist Infect Control **2024**; 13:19.
40. Wada YH, Ogunyinka IA, Yusuff KB, et al. Knowledge of Lassa fever, its prevention and control practices and their predictors among healthcare workers during an outbreak in Northern Nigeria: a multi-centre cross-sectional assessment. PLoS Negl Trop Dis **2022**; 16:e0010259.